BENEFIT OF SLOW INFUSION OF HYPERTONIC SALINE/DEXTRAN IN SWINE WITH UNCONTROLLED AORTOTOMY HEMORRHAGE

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ABSTRACT   In laboratory models of uncontrolled hemorrhage, immediate resuscitation from hemorrhage is associated with high mortality. However, in clinical practice, resuscitation is often delayed and the rate of fluid administration is limited. We hypothesized that a slow rate of infusion after delayed resuscitation, reflecting the clinical environment, might improve survival in the presence of uncontrolled hemorrhage. To investigate the rate of administration in the presence of delayed resuscitation, we subjected anesthetized swine weighing 35 to 45 kg to wire suture abdominal aortotomy that resulted in an uncontrolled hemorrhage. After a 30-min delay, hemorrhaged swine were infused i.v. with 4 mL/kg hypertonic saline/Dextran solution (7.5% saline in 6% Dextran 70) administered as a bolus over 1 min or as a slow infusion over 12 min (the time period to administer a similar volume to a human with a gravity feed i.v. and an 18-gauge needle) and were then monitored for another 90 min. Survival increased to 78% (seven of nine) in the slow infusion group compared with a survival rate of 56% (five of nine) in the bolus group and 50% (7/14) in the untreated controls. Blood loss was significantly higher in the bolus group (926 ± 77 mL) compared with the slow infusion (714 ± 83 mL) and control groups (604 ± 46 mL). Hypertonic saline/Dextran administered slowly significantly increased cardiac output and blood pressure. Taken together, these results are consistent with the hypothesis that resuscitation solutions can be effective for treatment of uncontrolled hemorrhage when administered at a slow infusion rate 30 min after the insult.

KEYWORDS   Hemorrhagic shock, fluid resuscitation, pigs

INTRODUCTION

Early (prehospital) aggressive intravenous administration of solutions such as lactated Ringer's (LR) complies with Advanced Trauma Life Support guidelines for the treatment of trauma and hypotension due to hemorrhage (1, 2). The rationale is that maintenance of plasma volume and blood pressure is necessary to ensure adequate perfusion of vital organs. However, Bickell et al. (3) questioned this practice. These authors concluded that in patients with hypotension resulting from penetrating torso injuries, delaying fluid resuscitation until the time of operative intervention improved outcome. As their conclusions have been challenged (4 6), it is clear that the timing for optimal fluid resuscitation remains controversial.

Leppaniemi et al. (7) demonstrated in an uncontrolled hemorrhage rat model that early and rapid administration of LR resulted in a higher mortality rate compared with animals resuscitated at lower infusion rates or after a delay. Other investigators (8 10) have also observed that normal saline could be effective in resuscitating uncontrolled hemorrhage in rats when administered after a 15-min delay. Stern et al. (11 14) suggested that survival after resuscitation with hypertonic saline solutions depended upon the time after injury when the fluids were administered and the rate at which they were given. Thus, the use of resuscitation fluids at some time after injury appears to be judicious.

Because of logistic constraints in delivering large volumes of fluid to the battlefield to resuscitate injured soldiers, over the past two decades our laboratory has investigated the use of hypertonic saline/Dextran (HSD; 7.5% NaCl in 6% Dextran 70) as a small volume resuscitation fluid to treat hemorrhagic shock. Maningas et al. (15) found that in an otherwise 100% lethal controlled blood loss in pigs (46 mL/kg over 15 min), resuscitation with HSD at a dose of 11.5 mL/kg produced 100% survival. Subsequent studies using animal models of controlled hemorrhage demonstrated that 4 mL/kg of HSD was effective in restoring hemodynamic variables to prehemorrhage levels and improving survival (16 20).

The rate of HSD infusion has been questioned for a number of reasons (21). In patients undergoing cardiac surgery, bolus infusion of a hypertonic/hyperoncotic solution led to an increase in preload compromising cardiac function (22). In anesthetized dogs, rapid administration of HSD induced cardiac arrhythmias and hypotension (23). Furthermore, chloriemic acidosis has also been implicated as a complication associated with rapid infusion of HSD (21). However, the possibility of increased bleeding and mortality with administration of fluids in the

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presence of uncontrolled hemorrhage has been of prime concern. Bickell et al. (24, 25) observed that in an aortotomy swine model of uncontrolled bleeding, which was 100% survivable if left untreated, HSD (at 4 mL/kg) and LR increased mortality when administered 6 min after initiation of injury and hemorrhage. Similar observations were made in rats in which early hypertonic saline (HS; 7.5%) infusion in a model of "uncontrolled" hemorrhagic shock led to an increased blood loss from injured vessels, a fall in mean arterial pressure (MAP), and higher mortality than in unresuscitated animals. If HS infusion was delayed, then mortality rates were reduced (25).

For injured patients, the initiation of treatment is often delayed after injury because of the response time of caregivers and initial evaluation of the patient. This delay has been reported to be about 30 min (26, 27). Thus, the question remains: What would be the effect of HSD in treating uncontrolled hemorrhage, if HSD were administered more gradually and at a more clinically realistic time, i.e., 30 min postinjury?

The present study used an uncontrolled hemorrhage aortotomy swine model (24, 28) with treatment delayed 30 min, to examine the hemodynamic response and mortality rate of gradual versus bolus infusion of HSD. Bolus and gradual infusions were compared to determine if one mode of administration is preferable.

MATERIALS AND METHODS

Experimental procedure

Thirty-two female swine weighing 28 to 45 kg were entered into the study. After an overnight fast, they were premedicated with an intramuscular injection of 2.2 mg/kg ketamine, 2.2 mg/kg xylazine, and 0.08 mg/kg atropine, followed by halothane anesthesia via a facemask. After endotracheal intubation, anesthesia was maintained with oxygen, 12% nitrous oxide, and 1% to 2% halothane via respirator. Under aseptic conditions, a neck incision was performed and a Swan-Ganz cannula was placed via the internal jugular vein for measurement of cardiac output, central venous, and pulmonary artery pressure. An external jugular catheter was inserted for injection and a carotid catheter was inserted for measuring systemic arterial pressure. A splenectomy was performed through a midline laparotomy with ligation of all vascular pedicles. The abdominal aorta was exposed, using warm saline-soaked towels to retract the viscera. The aorta was marked with two points 5 mm apart approximately 10 cm proximal to the iliac artery bifurcation. A 4-0 surgical wire was threaded through the ventral aortic wall, into the lumen, and back out again at these points using a curved 27-gauge needle as a guide. The free ends of the surgical wire were then exteriorized through a small hole in the abdominal wall and the abdominal incision was sewn closed. Other details of the surgical procedure have been described previously (24, 28). The experiments were performed in adherence to the National Institutes of Health Guidelines on the Use of Laboratory Animals and the study was approved by our Institutional Animal Care and Use Committee.

The nitrous oxide was discontinued and the animal spontaneously breathed a mixture of oxygen and 1.0% to 1.5% halothane. After a 10-min stabilization period, two control samples were taken 10 min apart. Samples consisted of hemodynamic data: systemic pressures and cardiac output. If the hemodynamic readings were unstable (did not agree within 10%), an additional 10-min period was allowed and measurements were retaken.

Aortotomy (hemorrhage) was then accomplished by pulling out the wire suture through the abdominal wall (24, 28). This caused a 5-mm slit-like tear in the long axis of the ventral abdominal aortic wall. Hemodynamic variables were measured 15 and 30 min after aortotomy. Animals were then randomly assigned to a treatment group. Treatment was begun immediately after the 30-min sample. Group A (the control group, n = 14), received no fluid. In Group B (slow infusion group, n = 9), HSD was administered slowly, at 4 mL/kg, over a period of 12 min. The 12-min period is the time necessary to deliver 4 mL/kg of a colloid solution to a 70-kg human through an 18-gauge angiocath with a standard i.v. set with a gravity feed of 91 cm. In Group C (bolus infusion group, n = 9), the same dose of HSD was administered in approximately 1 min. Hemodynamic measurements were made 15, 30, 60, and 90 min after the onset of treatment. The experimental duration of 90 min was selected as 95% of the deaths in this model occur within 60 min of the onset of resuscitation with limited mortality thereafter (24, 28). After the last measurement, humane euthanasia was performed on surviving animals with an overdose of

barbiturate. The abdominal incision was then reopened and the total blood loss into the abdominal cavity was estimated by volumetric measurement of all available free blood and clots.

Statistical analysis

The data were evaluated using an analysis of covariance with the 30-min post-aortotomy value (pretreatment) as the covariate. When the F ratio was significant, the Newman-Keuls test was used to identify the specific group and time differences. Reported values are expressed as means ± SEM. Differences in survival were analyzed using a chi-square test. Differences were considered significant at $P < 0.05$.

RESULTS

After aortotomy, a 30-min delay, fluid resuscitation, and 90 min of observation, survival was 50% (7/14) in untreated swine, 56% (5/9) in the bolus HSD group, and improved to 78% (7/9) in the slow infusion group. Survival was lower in those animals that were untreated or treated with HSD as a bolus compared with those administered HSD at a slow rate (Fig. 1). There was an increase in the amount of blood lost in the group receiving HSD as a bolus compared with untreated controls or animals administered HSD at a slow rate (Table 1 and Fig. 2).

As expected, MAP decreased markedly with aortotomy from 92 ± 6.9 mmHg at baseline to 42 ± 2.5 mmHg at 30 min of hemorrhage due to aortotomy (n = 32). There were no differences in blood pressure between groups after aortotomy and before resuscitation (Table 2). With fluid resuscitation, the bolus group showed no discernable increase in MAP when measured 15 min after infusion (Table 2). The slow infusion group, on the other hand, did show an increase in MAP, and this increase was sustained in survivors throughout the 90-min recovery period (Table 2). Cardiac output decreased predictably with aortotomy hemorrhage from 4.0 ± 0.48 L/min to 2.2 ± 0.29 L/min at 30 min (n = 32). Similar levels were observed in all groups before resuscitation (Table 2). With no treatment, cardiac output did not improve over the 90-min period of observation. Infusion of HSD, by slow infusion or as a bolus, improved cardiac output. Improvements from slow infusion were faster and greater. Bolus resuscitation was adequate in
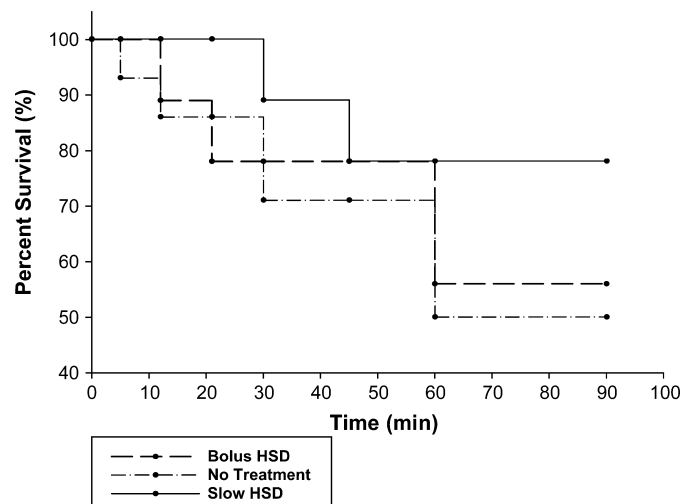

Fig. 1. **Percentage of animals surviving over time after resuscitation.** No treatment (n = 14), slow infusion of HSD, 4 mL/kg/12 min (n = 9), and bolus infusion of HSD 4 mL/kg/1 min (n = 9).

TABLE 1. **Number of animals, body weight, mean survival time, and blood loss**

Treatment	Number of animals	Body weight (kg)	Mean survival time (min)	Blood loss (mL)	Percentage of total blood volume lost
No treatment	14	36.3 ± 0.84	60 ± 9.4	604 ± 45.6	26 ± 2.2
Bolus infusion	9	35.0 ± 1.55	67 ± 10.5	926 ± 77.0*	40 ± 2.6*
Slow infusion	9	38.4 ± 1.92	78 ± 7.8	714 ± 82.5	29 ± 3.8

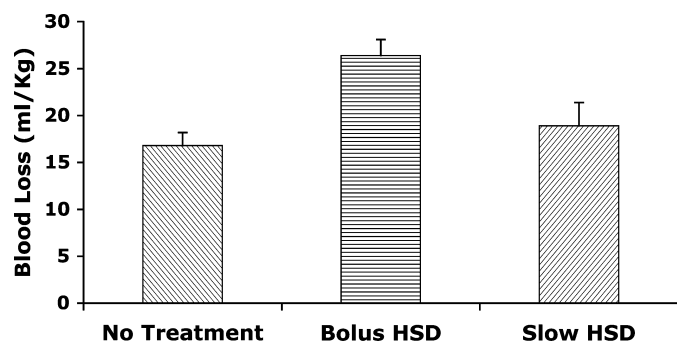An asterisk denotes significant differences among groups. Values are means ± SEM.

FIG. 2. **Blood volume loss in the area of the aortotomy.** Values are adjusted for the body weight of the animal. No treatment (n = 14), slow infusion of HSD (n = 9) and bolus infusion of HSD (n = 9). * denotes significant differences between groups. Values are means ± SEM.

improving cardiac output, but values dropped at 60 and 90 min. Neither infusion rate of HSD sustained cardiac output at prehemorrhage levels, but both improved cardiac output when compared with unresuscitated animals.

DISCUSSION

Restricting fluids resuscitation until attaining hemorrhage control makes sense when evacuation time is prolonged. As demonstrated by Capone et al. (29) in a study mimicking prehospital resuscitation, administration of fluids was necessary to improve survival in an uncontrolled hemorrhage model if the transport time was protracted.

Immediate (within 10 min of injury) resuscitation of hemorrhagic hypotension, associated with damage to a major blood vessel, tends to reinitiate significant bleeding independent of the type of fluid administered (8, 12, 13, 24, 28, 30). The sudden increase in blood pressure after an infusion of resuscitation solutions dislodges or disrupts the established thrombus. The increase in blood pressure, coupled with hemo-dilution induced by crystalloid or colloid fluid administration, would prevent reformation of the mural thrombus. Thus, timing of fluid resuscitation, as well as the rate of infusion, may impact blood loss and survival.

A number of studies of uncontrolled hemorrhage have shown that early resuscitation, whether with LR, HS, or HSD, causes increased bleeding and a decrease in survival (8, 12, 13, 24, 28, 30). The present study, on the other hand, allowed a 30-min delay for the thrombus to stabilize, and thus be more secure, before the increase in pressure caused by HSD resuscitation. A similar approach by others has shown benefit (12, 13), though recent studies have shown minimal effect of delaying resuscitation for up to 30 min (30). Sondeen et al. (30) in a study of pigs resuscitated with LR reported no difference in the incidence of bleeding with delays of up to 30 min after aortotomy

by a tissue defect. Resuscitation in this study was at rates of 2.5 or 7.5 mL/kg/min to an endpoint of induction of rebleeding. The incidence of rebleeding was a function of the increase in mean blood pressure above 65 mmHg irrespective of the delay time of fluid administration.

Delayed resuscitation studies are realistic in the sense that most clinical resuscitation is begun only after delays incurred from the time of injury to notification of authorities, during the response by health care providers, and initial evaluation and treatment of the patient at the scene of the incident (26, 27). We would estimate these delays to be minimally 30 min between time of injury and initiation of fluid resuscitation. Furthermore, the rate of fluid administration is often limited (31). In the present study, incorporating a 30-min delay in resuscitation with the administration of HSD as a bolus increased bleeding, but did not increase mortality compared with untreated controls. This is in contrast to earlier studies where immediate resuscitation increased mortality (28). In the present study, for delayed resuscitation with a bolus infusion, survival was 57% (5/9) compared with 38% (3/8) for immediate resuscitation in an earlier study by our group (28). This difference appears to be the result of a decrease in blood loss after delayed resuscitation, 926 ± 77 mL in the present study compared with 1340 ± 230 mL in the previous study (28). Thus, the delay in resuscitation appears to be beneficial as noted by others (7, 25).

In general, the hemodynamic data from the bolus infusion of HSD in the current study are consistent with the effects of HSD infusion administered as a bolus within minutes of aortotomy (12, 13, 28, 30). Nevertheless, in immediate and delayed administration for the treatment of uncontrolled hemorrhage, the data are markedly different from the hemodynamic effects of HSD infused as a bolus after controlled hemorrhage. In controlled hemorrhage, HSD given at the same dose as in the present study resulted in a marked increase in MAP and return of cardiac output to prehemorrhaged levels (6, 18, 19). In the present study, only the slow infusion resulted in an increase in MAP and cardiac output. However, neither blood pressure nor cardiac output was returned to prehemorrhage levels. The reason for the decrease in responsiveness of blood pressure and cardiac output appears related in part to the rate of administration. Thus, a slow rate of administration of HSD may attenuate the magnitude of previously reported improvements in cardiovascular function, and therefore oxygen delivery. Alternatively, bolus infusion of HSD may have caused an immediate and much greater increase in MAP, thus dislodging the clot, causing rebleeding and a rapid reduction of MAP to prere-suscitation levels when measured 15 min later.

It is interesting to note that in the present study, a 30-min delayed infusion of HSD at a slow rate resulted in blood loss similar to that in untreated controls. Thus, the results of the

TABLE 2. **MAP and cardiac output 30 min after aortotomy (preinfusion) and for 90 min after resuscitation**

	Preinfusion	15 min	30 min	60 min	90 min
MAP (mmHg)					
No treatment	40 ± 1.4	38 ± 1.4	41 ± 2.7	44 ± 4.4	44 ± 4.1
HSD bolus	43 ± 2.7	43 ± 2.7	43 ± 4.1	37 ± 4.1	41 ± 4.1
HSD slow	45 ± 4.1	59 ± 4.2*	59 ± 5.4*	62 ± 4.1*	56 ± 5.4*
CO (L/min)					
No treatment	2.0 ± 0.27	1.9 ± 0.21	1.9 ± 0.21	2.1 ± 0.21	2.2 ± 0.21
HSD bolus	2.4 ± 0.34	2.9 ± 0.41*	3.4 ± 0.48*	2.6 ± 0.48	2.9 ± 0.48
HSD slow	2.3 ± 0.27	4.2 ± 0.34*	3.4 ± 0.27*	3.5 ± 0.21*	3.1 ± 0.23*

Note that there was a reduction in the number of animals in each group over the course of the study (see Fig. 1).
An asterisk denotes significant differences compared with the "no treatment" group.
Values are means ± SEM.

current study would suggest that total blood loss is not increased if resuscitation with HSD occurs some time after injury and the fluid is administered at a slow rate, correcting hemodynamics. Krausz et al. (25) observed no difference in bled volume in rats infused with HS alone or HS followed by normal saline to sustain blood pressure, but survival was significantly higher in the group that received the combined therapy. Stern et al. (13) in a swine model mimicking uncontrolled hemorrhage demonstrated significant improvement in hemodynamics and subsequent survival with a slow rate of infusion (0.4 mL/kg/min) in contrast to a bolus (1.33 mL/kg/min) of HSD. In the present study, compared with untreated animals, slow infusion of HSD (0.34 mL/kg/min) resulted in no difference in blood loss, greater hemodynamic improvement, and a trend toward a higher survival rate. Thus, in our model, there were advantages to slow resuscitation with HSD at a rate that would been seen with an 18-gauge needle and standard intravenous infusion set, in contrast to withholding treatment.

It should be pointed out that not all studies have been successful in treating uncontrolled hemorrhage with hypertonic solutions. Using a rat model in which the ileocolic arteries were severed, Gross et al. (32) injected 5 mL/kg HS at various times up to 2 h after insult. They reported further decreases in MAP and mortality rates that exceeded those of untreated controls irrespective of the time of the delay in resuscitation. One difference between their study and ours was that we included colloid in the infusion solution, which may account for the difference in results. Reed et al. (33) reported that HS could increase plasma-clotting times and decrease platelet aggregation. We also observed a similar effect of HS on prothrombin times and platelet aggregation *in vitro* (34), but *in vivo*, the addition of the colloid (HSD) infusion did not affect these variables or prolong bleeding times (35). Also, in the study by Gross et al. (32), if the walls of the vessels had simply been incised, like those of the aorta in the present study, instead of the vessels being completely transected, it is possible that more stable clots could have formed and the results might have been similar to those of the present study.

To summarize, the results of the current study are compatible with the hypothesis that HSD is an effective resuscitation solution in the treatment of uncontrolled hemorrhage when administered 30 min after the insult and at a slow rate of infusion. This study is unique as we used an injury to induce hemorrhage and used a realistic period of delay before initiation resuscitation. In this model of injury where bleeding is not controlled, the use of HSD at a slow infusion rate was beneficial. However, as the treatment results in a level of hypotension that may not be sustainable for an extended period, further investigation is indicated (36).

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